Docket No: 2685.3002 US
Expedited Procedure under 37 C.F.R. 1.116
Examining Group 1614

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Elliot Ehrich, Daniel Deaver, Robert Clarke and Michael M. Lipp

Application No: 10/550,471 Group No: 1614

Filed: September 1, 2006 Examiner: Gregg Polansky

Confirmation No.: 4421

Title: Trospium Containing Compositions

APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Brief is being filed pursuant to 37 CFR 41.37. The fee under 37 CFR 41.20(b)(2) is filed herewith. The required sections under 37 CFR 41.37 are set forth below under separate headings.

(1) The Real Party of Interest

The real party of interest in this appeal is Alkermes, Inc. by virtue of the Assignment recorded on June 2, 2009 at Reel 022764 and Frames 0088-0103.

(2) Related Appeals and Interferences

There are no related appeals or interferences at this time known to the appellant, the assignee or its representative which will directly affect or be directly affected by or have a bearing in the Board's decision in the pending appeal.

(3) Status of the Claims

Paragraph 10 of the Final Office Action dated January 23, 2009, states that claims 1, 2, 4-8, 10-16 and 18-28 are rejected. However the Final Office Action sets forth grounds of rejection for *only* claims 1-2, 4-8, 10-13, 15, and 18-28. No ground of rejection for claims 14 and 16 has been set forth in the Final Office Action, as required under MPEP 707.07(i). It is believed that the statement that claims 14 and 16 are "rejected" is a clerical error. Given the absence of any rejection or objection and that the claims were examined, it is believed that these claims are allowable but should be "objected to" as being dependent upon a rejected base claim. MPEP 608.01(n), last paragraph.[1] Therefore it is believed that claims 1-2, 4-8, 10-13, 15, and 18-28 are pending and finally rejected. Claims 3, 9 and 17 were cancelled during prosecution. No claims are withdrawn from consideration. Claim 28 is **not** appealed. **Claims 1-2, 4-8, 10-16 and 18-27 are appealed**.

(4) Status of the Amendments

No claim amendments after Final Rejection were filed.

(5) Summary of Claimed Subject Matter

Claim 1 recites a method for treating a disease characterized by a constrictive airway comprising administering to a patient in need thereof via inhalation a pharmaceutical composition comprising trospium, wherein said patient achieves an effective therapy for at least 10 hours. Support for claim 1 is found on page 2, lines 24-27. Claim 2 depends from claim 1 and recites that the disease to be treated is chronic

[1] It should also be noted that claims 15 and 18-20 depend from claims 14 and 16. Because a proper dependent claim cannot be properly considered anticipated or obvious if the claim from which it depends is novel and non-obvious these claims should also be the subject of an objection and that the statement that they are rejected is a clerical error. This will be addressed in more detail below.

obstructive pulmonary disease (page 2, lines 30-31). Claim 4 depends from claim 1 and recites that the composition comprises a dose of trospium of between about 200-800 mcg (page 3, line 13). Claim 5 depends from claim 1 and recites that the composition comprises an aqueous solution of trospium hydrochloride (page 3, lines 15-18). Claims 6 depends from claim 1 and recites that the composition comprises a particulate formulation comprising trospium (page 3, line 19). Claim 7 depends from claim 1 and recites that the composition comprises a particulate formulation of trospium administered by dry powder inhaler (page 3, line 20). Claim 8 depends from claim 1 and recites that the composition comprises a fine particle fraction of at least 50% (page 3, line 32). Claim 10 depends from claim 8 and recites that the trospium formulation is spray dried (page 3, lines 24-25). Claim 11 depends from claim 10 and recites that the formulation has a tap density of less than 0.4 g/cm^3 (page 3, line 28). Claim 12 depends from claim 11 and recites that the mass mean aerodynamic diameter is less than 5 microns (page 3, line 31).

Claim 13 depends from claim 12 and recites that the trospium formulation further comprises, leucine, phospholipid or combinations thereof (page 4, lines 4 and 10). Claim 14 depends from claim 13 and recites that the formulation comprises at least about 70% leucine (page 4, line 9). Claim 15 depends from claim 14 and recites that the formulation comprises less than 10% by weight of trospium (page 4, line 27). Claim 16 depends from claim 14 and recites that the formulations comprise about 5% by weight of trospium hydrochloride, between about 5 and 10% by weight of phospholipid and between about 85 and 90% by weight of leucine (page 4, lines 30-32). Claim 18 depends from claim 16 and recites that the dose of trospium administered is about 200 to 800 mcg (page 3, line 14). Claim 19 depends from claim 16 and recites that the patient achieves effective therapy for at least 15 hours (page 2, line 28) and claim 20 depends from claim 16 and recites that the patient achieves effective therapy for at least 24 hours (page 2, line 28). Claim 21 depends from claim 8 and recites that the formulation is administered once per day (page 2, line 20).

Claim 22 depends from claim 1 and further comprises administration of a second active agent (page 5, line 1). Claim 23 depends from claim 22 and recites that the second active agent is a beta-2 agonist (page 5, line 4). Claim 24 depends from claim 23 and recites that the second active agent is formoterol (page 5, line 4). Claim 25 depends from

claim 23 and recites that the second active agent is administered separately from the trospium formulation (page 5, lines 5-6). Claim 26 depends from claim 24 and recites that the second active agent is incorporated into the trospium formulation (page 5, line 10). Claim 27 depends from claim 24 and recites that the composition is spray dried comprising trospium, formoterol, leucine and optionally a phospholipid (page 5, lines 20-24).

(6) Grounds of Rejection to be Reviewed on Appeal

- That the Examiner has failed to show that claims 1, 4, 5, and 22-26 are anticipated under 35 U.S.C. §102(b) by Freund et al. (U.S. Pat. App. Pub. No. 2001/0008632).
- That the Examiner has failed to show that claims 1, 2, 4, 5, and 22-26 are unpatentable over Freund (U.S. Pat. App. Pub. No. 2001/0008632) in view of Richards (U.S. Patent Application Pub. No. 2003/0158176).
- That the Examiner has failed to show that claims 1-2, 4-8, 10-13, 15 and 18-27 are unpatentable over Freund (U.S. Pat. App. Pub. No. 2001/0008632) in view of Richards (U.S. Patent Application Pub. No. 2003/0158176) and further in view of Bernstein (U.S. Patent Application Pub. No. 2004/0105821).

(7) Argument

Claims 8, 10-16 and 18-27 do **not** stand or fall with claims 1-2 and 4-7 as will be discussed further for each claim in the arguments below under each ground of rejection.

A. Claim Rejections 35 U.S.C. §102

Claims 1, 4, 5 and 22-26 are rejected under 35 U.S.C. §102(b) as being anticipated by Freund et al. (U.S. Pat. App. Pub. No. 2001/0008632). The Examiner states that Freund teaches aqueous aerosols of anticholinergic agents including trospium chloride, ipratropium bromide, formoterol and fenoterol for inhalation in the treatment of respiratory passage diseases. The Examiner also states that Freund also teach an active agent concentration range of 10 mg/100ml to 2000 mg/100 ml and a nebulizer delivering 12 ml of concentrate per operation which the Examiner has calculated to be between 1.2 mcg and 2400 mcg per operation. The Examiner further notes that claim 1 of the instant application recites a functional limitation of "effective therapy of at least 10 hours" and that the instant

specification appears to demonstrate that both aqueous and dry powder formulations of trospium are therapeutically effective for at least 10 hours. The Examiner concludes that it appears that the 10 hour effective duration of action of trospium is independent of its formulation and one would anticipate that the aqueous trospium formula taught by Freund would have a similar therapeutically effective duration of action, absent evidence to the contrary. Appellants respectfully disagree.

For a reference to be anticipating, each and every claim limitation as set forth in the claim must be found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). In general, it is well accepted that a broad generic disclosure is insufficient to provide an anticipating disclosure. Where "it is necessary to select portions of teachings within a reference and combine them, e.g. select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can be found if the classes of substituents are sufficiently limited or well delineated. MPEP Section 2131.02, citing *Ex parte A*, 17 USPQ 2d 1716 (BPAI 1990). The MPEP goes on to discuss *In re Petering*, 301 F.2d 676 (CCPA 1962). In that case, it was held that the broad generic disclosure was insufficient to anticipate the claimed compounds in view of the six variables (note that five of the variables were each selected only from hydrogen and alkyl) as a nearly infinite number of compounds were potentially claimed. The anticipating disclosure relied upon the fact that the *preferred* subgenus narrowed three of the variables to a single option, i.e., hydrogen, two variables to two options, i.e. hydrogen or methyl, and the sixth variable to one of eight groups. Only *twenty* compounds were found to be embraced by the preferred subgenus. Where, as here, the reference does not offer any guidance to choose among long lists and various ranges, anticipation cannot be found, particularly where the selection requires selecting outside the preferred embodiments. Indeed, a broad generic disclosure is often insufficient to establish that a claim is obvious. *In re Baird*, 16 F.3d 380 (Fed. Cir. 1994). As will be described below, the broad generic disclosure of this patent does not lead one of ordinary skill in the art to select the specific combination of the claimed invention.

In this case, while Freund generically teaches aqueous medicament preparations, there is no specific teaching of a specific trospium formulation at a specific concentration

that will achieve a sustained or long acting therapy. Trospium is taught only in a long list of over one hundred different and diverse drugs. Trospium is not specifically exemplified. The composition specifically requires a complexing agent to prevent "spraying anomalies." The impact of these complexing agents on the pharmacokinetics of the drug is not described in the patent. While a broad range of concentrations are said to be "conceivable for the active ingredients" [Para. 0052], the specific dose which is to be effective for any specific drug is not taught. The context of this sentence is that the person of ordinary skill in the art would select an effective dose dependent on the specific drug and the specific result to be achieved assuming a delivery of 12 microliters of the formulation. Clearly, this reference fails to teach a trospium containing formulation containing an amount of trospium effective to provide an effective therapy for 10 hours. This reference relies on the person of skill in the art to *know* what the dose of any drug *should be* to achieve a desired therapy, to then calculate the amount required to be present in 12 microliters and then determine the concentration of the drug in the formulation.

In the Final Office Action the Examiner disagrees, asserting that the species is clearly named in Freund in a list of 4 anticholinergic agents (citing *Ex part A*, 17 USPQ 1716 (Bd. Pat. App. & Inter. 1990)). The Examiner's attempt to recharacterize the fact that more than one hundred drugs are taught equally by looking at the number of drugs listed in a smaller listed subgenus does not negate the general teachings of this reference. This reference is not about delivering anticholinergic agents and the treatment of related diseases. The reference is not about trying to make a long acting anticholinergic medicament. The reference is about stabilizing aqueous formulations to prevent "spraying anomalies" generally applicable to any nebulized drug.

It does not logically follow that simply because trospium is described in a long list and the reference satisfies that single claim limitation, that all of the claim limitations are satisfied. The limitation that the composition be long acting is simply not present and the Examiner has offered no scientific reason as to why such an effect will flow from all trospium compositions. Yes, Freund gives a generalized dosage range from 10 mg to 20,000 mg/100 ml for all 100 drugs. This dosage range is huge. Certainly one of skill in the art would not conclude from this range that all 100 drugs are effective across the entire range and that this range is equally applicable to each and every drug.

It may be true that, if trospium is added to the Freund formulation across this entire range of concentrations, one or more formulations may achieve a 10 hour effective therapy. However, even if that is true, it does not follow that the selection of trospium and the dose that achieves the claimed method is immediately envisioned by the person of skill in the art. The present claims are not anticipated by the mere presentation of a list of 100 or more drugs together with the statement that an effective dose of any such drug can be selected. A long acting therapy is not the inherent result of any effective dose of trospium. It requires the selection of a long acting dose of trospium.

While Appellants have shown that the 10 hour duration of therapeutic effectiveness can be achieved with both an aqueous formulation and a dry powder formulation, this is not tantamount to a showing that all aqueous or dry powder formulations comprising trospium inherently achieve this same effect. As shown in Figure 1b, there is a dose-dependent response associated with trospium formulations of various doses. As shown in Figure 1b, certain trospium formulations containing doses as low as 1 and 2 mcg (in the absence of a complexing agent) when administered according to the methods described in the specification begin to lose their broncoprotection at 5 hours and the 1 mcg dose is almost back at the pre-TrCl treatment baseline by 15 hours. This evidence makes clear that not all trospium formulations will achieve the claimed result. In relying on the theory of inherency, the Examiner must provide a factual basis to reasonably support that the allegedly inherent characteristic necessarily flows from the teachings of the cited reference each and every time; the mere fact that a certain thing may result from a given set of circumstances is simply not sufficient (MPEP §2112; *Ex parte Levy*, 17 USPQ2d 1461 (Bd. Pat. App. & Inter. 1990); *In re Robertson*, 169 F.3d. 743, 745 (Fed Cir. 1999). The skilled person would not necessarily choose trospium from amongst the list of over 100 drugs named in Freund on the one hand and would also not necessarily choose the dosage ranges which would provide the claimed 10 hour therapeutic benefit on the other hand. Indeed, there is no reason in this document to suppose that the 10 hour therapeutic benefit would be desirable.

In the Final Office Action, the Examiner asserts that "the relationship of the dose of trospium and the duration of action is a characteristic of trospium" and that since Freund teach a dose range which encompasses the instantly claimed dose range, the duration of

action of trospium as taught by Freund would be the same as the instant invention. Appellants respectfully disagree. It is well known that dose response, particularly duration of action, in drugs is dependent upon many factors including formulation, drug-drug interactions and the like. As evidenced by Bernstein, for example, the dose response such as duration of action are expected to be dependent upon other factors, in addition to the drug's properties, such as other components in the drug formulations or other drugs in the body that may enhance or diminish duration of action. It is noted that the Examiner concedes that such is the case in his characterization of Richards (below). Thus, the Examiner's assumption is simply factually incorrect. Furthermore, even if the Examiner was factually correct, it does not mean that the claimed method is legally anticipated under the doctrine of inherency, for the reasons set forth above.

Therefore, Appellants maintain the position that providing a trospium formulation having the claimed duration of action does not necessarily result from the teachings of Freund and the Examiner has failed to establish that Freund inherently anticipates the presently claimed invention. Withdrawal of the rejection under this section in view of Freund is respectfully requested.

Claim 4

Claim 4 depends from claim 1 and requires a specific dose of trospium. While Freund generically provides a broad dosage range for the disclosed drugs (about 12 microliters at a concentration of 10 mg to 2000 mg drug per 100ml), and 200 to 800 micrograms (the claimed range) falls within the prior art range, that fact alone does not justify anticipation. As discussed in MPEP 2131.03,

> When the prior art discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, and the reference teaches a broad range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. See, e.g.,

> *Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) wherein the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. Further, while there was a slight overlap between the reference's preferred range (150-350 degrees C) and the claimed range, that overlap was not sufficient for anticipation. "[T]he disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." *Id.* at 1000, 78 USPQ2d at 1424.

Using the MPEP as guidance and looking at the specific example of the claimed/prior art ranges that were found to not be anticipating (i.e., 100-500 °C did not anticipate 330-450 °C), more is required in this rejection to explain why the Examiner deems the claimed range to be anticipated (i.e., 1.2-2,400 micrograms[2] does not anticipate 200-800 micrograms). As such, the rejection of Claim 4 should be reversed.

Claim 22

Claim 22 depends from claim 1 and recites that the trospium is delivered with a second active agent. Freund does not disclose a species wherein trospium is delivered in combination with a second active agent. As discussed above, Freund lists at least 100 drugs that can be delivered singly or in combination (paragraph [0014] to paragraph [0045]). No specific combination species are named in Freund. Indeed over 10,000 dual drug combinations are theoretically described. There is no basis for selecting trospium specifically and adding yet another drug to that formulation. For the reasons discussed above, no trospium-containing combination is disclosed or suggested that will result in 10 hours duration of therapy. Thus the skilled person can not immediately envisage a combination of trospium and a second active agent having the presently claimed duration of therapy. Therefore, claims 22-26 are not anticipated by Freund. Withdrawal of the rejection is respectfully requested.

Claim 23

Claim 23 depends from claim 22 and recites that the trospium is delivered with a beta-2 agonist. Freund does not disclose a species wherein trospium is delivered in

[2] The undersigned has not verified the Examiner's conversions.

combination with a beta-2 agonist. As discussed above, Freund lists at least 100 drugs that can be delivered singly or in combination (paragraph [0014] to paragraph [0045]). No specific combination species are named in Freund. Indeed over 10,000 dual drug combinations are theoretically described. There is no basis for selecting trospium specifically and adding a beta-2 agonist to that formulation nor is it disclosed or suggested that will result in 10 hours duration of therapy. Thus the skilled person can not immediately envisage a combination of trospium and a beta-2 agonist having the presently claimed duration of therapy. Therefore, claim 23 is not anticipated by Freund. Withdrawal of the rejection is respectfully requested.

Claim 24

Claim 24 depends from claim 23 and recites that the trospium is delivered with a formoterol. Freund does not disclose a species wherein trospium is delivered in combination with formoterol. While both trospium and formoterol are listed in the same 100+ drug list, there is no basis for concluding that this very specific combination would be chosen out of the over 10,000 dual drug combinations theoretically described. Nor is it disclosed or suggested that will result in 10 hours duration of therapy. Therefore, claim 24 is not anticipated by Freund. Withdrawal of the rejection is respectfully requested.

Claim 25

Claim 25 depends from claim 23 and recites that the trospium and the beta-2 agonist are administered separately. The Examiner does not even attempt to state where this limitation is found in Freund. Because Freund is not concerned with the actual treatment of a patient but is concerned with formulation stability, it does not teach this limitation and the rejection is clearly improper. Therefore, claim 25 is not anticipated by Freund. Withdrawal of the rejection is respectfully requested.

Claim 26

Claim 26 depends from claim 24 and recites that the trospium and formoterol are incorporated into the same formulation. Again, the Examiner does not show where this limitation is found. While both trospium and formoterol are listed in the same 100+ drug

list, there is no basis for concluding that this very specific combination would be chosen out of the over 10,000 dual drug combinations theoretically described. Nor is it disclosed or suggested that it will result in 10 hours duration of therapy. Therefore, claim 26 is not anticipated by Freund. Withdrawal of the rejection is respectfully requested.

B. Claim Rejections-35 U.S.C. §103: *Rejection over Freund in view of Richards*

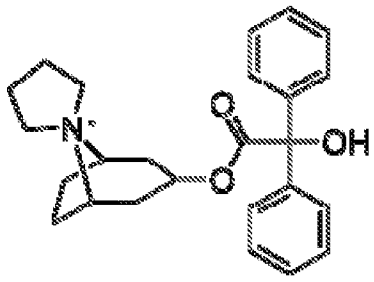
The Examiner has rejected claims 1, 2, 4, 5, and 22-26 under 35 U.S.C. §103(a) as being unpatentable over Freund (U.S. Pat. App. Pub. No. 2001/0008632) in view of Richards (U.S. Patent Application Pub. No. 2003/0158176). The Examiner relies on Freund's teachings above. Referring to claim 2, the Examiner states that Freund does not teach specific respiratory passage disease. The Examiner asserts that Richards teaches that anticholinergic (antimuscarinic) agents which include trospium are useful in the treating COPD. The Examiner also states that Richards teaches that the dose depends on many factors including potency of the compound, the age and weight of the patient and the severity of the disease. The Examiner asserts that one of ordinary skill would have optimized the dose taught by Freund to maximize the therapeutic effects and minimize the deleterious effects of the active agent. The Examiner then states that the skilled person would have found it obvious to combine these two teachings to treat diseases such as COPD by inhalation of trospium because Freund teaches the usefulness of trospium and formoterol for treating respiratory passage disease and Richards teaches COPD and asthma as two respiratory diseases effectively treated by trospium. The Examiner concludes that one would have been motivated to administer the active agents via inhalation to treat the respiratory system to minimize the amount of agent administered systemically thereby avoiding undesirable effects and to improve upon the known methods of treatment for COPD and asthma.

Claim 1

Freund is discussed above. The Examiner has not provided motivation as to why one would pick trospium from a list of over 100 active ingredients disclosed in paragraphs 0015-0045 of Freund in order to prepare an optimized formulation having sustained effective therapy for at least 10 hours. The Examiner asserts in response that Richards

teaches trospium to be an anticholinergic agent and provides ample motivation to select trospium as one of 4 anticholinergic agents disclosed by Freund as an active agent in the Freund reference.

Actually, trospium is not the compound formulated or tested in Richards. Trospium is an anti-muscarinic and has the structure:



Richards discloses the synthesis and testing of novel anti-muscarinics that are very different from trospium. Richards simply teaches nothing about dosage or formulation or hours of therapeutic effectiveness of *trospium*. Anti-muscarinics belong to a functional class definition. Compounds that behave as anti-muscarinics are diverse structurally and functionally even with regard to their anti-muscarinic activity and potency. Thus the bronchodilatory effects of various dosages and formulations of trospium are not and cannot be disclosed in Richards. Given the compounds in Richards are very different from trospium there is no basis for the Examiner's assumption that Richards provides any useful information with regard to the optimization of dosages and formulations of *trospium* which achieve effective therapy for at least 10 hours, alone or in combination with Freund.

Freund does not teach or disclose the therapeutic effectiveness or hours of therapeutic effectiveness of any of the active ingredients listed therein. Freund's alleged discovery is that the spraying anomalies of aqueous pharmaceutical solutions for inhalation using a nebulizer can be reduced or minimized by the use of a complexing agent in the aqueous preparation. The therapeutic effectiveness of the solutions prepared by Freund was not tested. Only the ability of EDTA to minimize nebulizer anomalies in formulations containing drugs other than trospium is tested.

One of ordinary skill in the art would simply not be motivated to combine these references. Even if one were to combine these references, the person of skill in the art

would likely choose to formulate the compounds of Richards in an aqueous formulation containing complexing agents to avoid spraying anomalies in accordance with the teachings of Freund, that achieve pharmacokinetic profiles as taught in Richards, and that treat the diseases taught by Richards. There is no reason to believe that a person of skill in the art would choose to formulate trospium with the expectation that it would behave like the structurally distinct compounds of Richards and then optimize that formulation.

Claim 2

In the Final Office Action, the Examiner states that Richards was provided to demonstrate prior art knowledge of the use of anticholinergic agents in the treatment of acetylcholine mediated disorders such as COPD. The Examiner asserts that the rejection does not depend upon a teaching by Richards of dosage, formulation or hours of therapeutic effectiveness. The Examiner states that Richards is relied upon to teach that antimuscarinic agents can treat COPD and that teaching provides motivation for the skilled artisan to select trospium from Freund as an active agent and to use it to treat COPD.

Appellants appreciate and understand the Examiner's reasons in this regard. However as Appellants have discussed previously, it is simply not enough that the Examiner identify that others use antimuscarinic agents in the treatment of COPD. The Applicant's invention is the unexpected duration of therapy in the treatment of COPD using a *specific* antimuscarinic, trospium, not just any antimuscarinic. Richards' discloses and tests an entirely different compound the results of which have no bearing on the duration of therapy of specific formulations comprising trospium. As discussed with regard to Freund in the §102 rejection, Freund simply does not provide the skilled person with any guidance with regard to identifying a formulation of any drug that results in 10 hours duration of therapy. The claim limitation is simply not present in Freund either explicitly or inherently for the reasons discussed previously and the limitation is also not present in Richards. Therefore, the combination of Freund and Richards does not disclose or suggest all of the claim limitations of claims 1 and 2, for example.

In view of the above discussion, the Examiner has failed to establish that the presently claimed invention is *prima facie* obvious in view of the cited combination of references. Withdrawal of the rejection under this section is respectfully requested.

Claim 4

Claim 4 and Freund is discussed above. Richards teaches that the compounds described therein can be delivered to a human in an amount between 1 microgram and 1 mg. [Para. 0108] Even if one were to assume that the dose for trospium is identical to the dose of Richards' compounds (which is itself an justified assumption), this range does not teach the specific range described. There is no reason to believe that the trospium dose of claim 4 will achieve a long acting therapy. Therefore, it is non-obvious on this record.

Claim 22

Claims 22-26 include all of the limitations of claim 1. For the reasons discussed in detail above with respect to claim 1, claims 22-26 are not made obvious by the combination of Richards and Freund. There is no motivation provided by either reference to seek a formulation of trospium particularly one that provides 10 hours of therapy as discussed above, and there is no suggestion or motivation to combine trospium with any other active agent, such as beta-2 agonists or formoterol, while maintaining the claimed duration of therapy of trospium. Just as Fruend does not teach these combinations, Richards does not. Withdrawal of the rejection of claims 22-26 under this section is respectfully requested.

Claim 23

Claim 23 depends from claim 22 and recites that the trospium is delivered with a beta-2 agonist. Neither Freund nor Richards disclose a species wherein trospium is delivered in combination with a beta-2 agonist. As discussed above, Freund lists at least 100 drugs that can be delivered singly or in combination (paragraph [0014] to paragraph [0045]). No specific combination species are named in Freund. Indeed over 10,000 dual drug combinations are theoretically described. There is no basis for selecting trospium specifically and adding a beta-2 agonist to that formulation nor is it disclosed or suggested that it will result in 10 hours duration of therapy. Richards adds nothing to the teachings of Freund. Thus the skilled person can not immediately envisage a combination of trospium and a beta-2 agonist having the presently claimed duration of therapy. Therefore, claim

23 is not obvious over these references. Withdrawal of the rejection is respectfully requested.

Claim 24

Claim 24 depends from claim 23 and recites that the trospium is delivered with formoterol. Freund does not disclose a species wherein trospium is delivered in combination with formoterol. While both trospium and formoterol are listed in the same 100+ drug list, there is no basis for concluding that this very specific combination would be chosen out of the over 10,000 dual drug combinations theoretically described. Nor is it disclosed or suggested that will result in 10 hours duration of therapy. Richards adds nothing to this teaching. Therefore, claim 24 is not obvious over Freund and Richards. Withdrawal of the rejection is respectfully requested.

Claim 25

Claim 25 depends from claim 23 and recites that the trospium and the beta-2 agonist are delivered separately. The Examiner does not even attempt to state where this limitation is found in Freund. Because Freund is not concerned with the actual treatment of a patient but is concerned with formulation stability, it does not teach this limitation and the rejection is clearly improper. Richards adds nothing to this teaching. Therefore, claim 25 is not obvious over Freund and Richards. Withdrawal of the rejection is respectfully requested.

Claim 26

Claim 26 depends from claim 24 and recites that the trospium and formoterol are incorporated into the same formulation. Again, the Examiner does not show where this limitation is found. While both trospium and formoterol are listed in the same 100+ drug list, there is no basis for concluding that this very specific combination would be chosen out of the over 10,000 dual drug combinations theoretically described. Nor is it disclosed or suggested that it will result in 10 hours duration of therapy. Richards adds nothing to this teaching. Therefore, claim 26 is not obvious over Freund and Richards. Withdrawal of the rejection is respectfully requested.

C. Claim Rejections-35 U.S.C. §103: *Rejection over Freund in view of Richards and Bernstein*

The Examiner has rejected claims 1-2, 4-8, 10-13, 15 and 18-28 under 35 U.S.C. §103(a) as unpatentable over Freund (U.S. Pat. App. Pub. No. 2001/0008632) in view of Richards (U.S. Patent Application Pub. No. 2003/0158176) as applied to claims 1, 2, 4, 5, 22-26 and 28 above, and further in view of Bernstein (U.S. Patent Application Pub. No. 2004/0105821). Freund and Richards are discussed above. The Examiner states that Bernstein teaches particulate sustained release pharmaceutical formulations for inhalation useful in treating asthma and COPD among others. Bernstein teaches the encapsulation of a drug to provide a sustained release profile.

The Examiner states that the sustained release formulation provides local or plasma concentrations at nearly constant values over a period of release allowing patients to take the treatments one or twice daily. The Examiner notes that although Bernstein does not teach trospium *per se*, they do teach anticholinergic agents in general and that Freund discloses trospium and ipratropium. The Examiner asserts that one of ordinary skill in the art would have understood (especially in light of the teaching of Freund) that one known anticholinergic agent (i.e. trospium) could be substituted for another (i.e. ipratropium) with reasonable expectation of success. Appellants disagree.

Freund does not teach or disclose the therapeutic effectiveness or hours of therapeutic effectiveness of the active ingredients listed therein. Freund's alleged discovery is that the spraying anomalies of aqueous pharmaceutical solutions for inhalation using a nebulizer can be reduced or minimized by the use of a complexing agent in the aqueous preparation. The therapeutic effectiveness of any of the solutions prepared by Freund is never tested. Only the ability of the complexing agent to minimize nebulizers with spray anomalies is tested with a formulation of ipratropium bromide and EDTA. Note that the other solutions of active ingredients listed in the table in paragraph 0051 are not even tested for nebulizer anomalies. Clearly one skilled in the art would not have "understood" that one anticholinergic agent such as trospium could be substituted with another such as ipratropium with any reasonable expectation of therapeutic effectiveness for any time frame based on Freund.

Likewise, Bernstein is directed to particle formulation and does not provide any evidence of the therapeutic effectiveness of any the hundreds of therapeutic agents listed therein. Only the physical characteristics of the particles prepared therein are tested in the Examples disclosed and then only the regional distribution of particles containing budesonide in the human lung is tested in Example 4. Bernstein provides no information or evidence with regard to the therapeutic effectiveness or hours of therapeutic effectiveness of the formulations or whether such formulations actually provide the extended release properties asserted in Bernstein. Further, Bernstein suggests that in order to provide a long acting formulation, one should encapsulate the drug into a sustained release matrix. The present inventors found this to not be necessary.

Furthermore, Richards never tests *trospium* for therapeutic effectiveness over any period of time. As discussed above, Richards tests compounds having chemical structures that are entirely different from trospium. Therefore, the skilled person has no basis to conclude that an inhalable trospium formulation is capable of delivering 10 hours of effective therapy based on the cited combination of references.

In the Final Office Action, the Examiner points out that Bernstein was provided for the teaching of particulate sustained release pharmaceutical formulations of anticholinergics for inhalation and the use of such dry powder formulations in the treatment of respiratory diseases including COPD. As discussed previously, it is simply not sufficient that Bernstein disclose that certain dry particle formulations of one specific anticholinergic (ipratropium bromide), which is named but never tested provides the limitation regarding duration in therapy that is lacking in both Freund and Richardson as discussed above. To establish a *prima facie* case of obviousness, the prior art reference (or references) when combined must teach or suggest all of the claim limitations (MPEP §2143).

Further, one of skill in the art would simply not combine Bernstein with Freund. Freund is directed to preventing spraying anomalies of a solution in a nebulizer. Bernstein is directed to making a dry powder for a dry powder inhaler or a suspension. See the Abstract. These are very different problems and the solution in Freund would not be applicable to the powders of Bernstein. One would look to Richards and conclude that the long acting compounds therein do not require the technology of Bernstein.

The Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, withdrawal of the rejection under this section in view of the cited references is respectfully requested.

Claim 2

In the Final Office Action, the Examiner states that Richards was provided to demonstrate prior art knowledge of the use of anticholinergic agents in the treatment of acetylcholine mediated disorders such as COPD. The Examiner asserts that the rejection does not depend upon a teaching by Richards of dosage, formulation or hours of therapeutic effectiveness. The Examiner states that Richards is relied upon to teach that antimuscarinic agents can treat COPD and that teaching provides motivation for the skilled artisan to select trospium from Freund as an active agent and to use it to treat COPD.

Appellants appreciate and understand the Examiner's reasons in this regard. However as Appellants have discussed previously, it is simply not enough that the Examiner identify that others use antimuscarinic agents in the treatment of COPD. The Appellant's invention is the unexpected duration of therapy in the treatment of COPD using a *specific* antimuscarinic, trospium, not just any antimuscarinic. Richards' discloses and tests an entirely different compound the results of which have no bearing on the duration of therapy of specific formulations comprising trospium. As discussed with regard to Freund in the §102 rejection, Freund simply does not provide the skilled person with any guidance with regard to identifying a formulation of any drug that results in 10 hours duration of therapy. The claim limitation is simply not present in Freund either explicitly or inherently for the reasons discussed previously and the limitation is also not present in Richards.

Bernstein adds nothing to this discussion. Therefore, the combination of Freund, Richards and Bernstein does not disclose or suggest all of the claim limitations of claims 1 and 2, for example.

In view of the above discussion, the Examiner has failed to establish that the presently claimed invention is *prima facie* obvious in view of the cited combination of references. Withdrawal of the rejection under this section is respectfully requested.

Claim 4

Claim 4, Freund and Richards is discussed above. Richards teaches that the compounds described therein can be delivered to a human Bernstein does not teach effective amounts for trospium. There is no reason to believe that the trospium dose of claim 4 will achieve a long acting therapy. Therefore, it is non-obvious on this record.

Claims 7 and 8

Claims 7 and 8 include all of the limitations of claim 1 and recite that the composition comprises a dry particulate formulation of trospium (claim 7) characterized by a fine particle fraction of at least 50% (claim 8) and wherein the formulation is administered with a dry powder inhaler. Fine particle fraction is defined on page 3, line 32 to page 4, line 2 as having an aerodynamic diameter of less than 3.4 microns as determined with an 8 stage cascade impactor. Freund, the primary reference does not disclose spray-dried formulations at all. Indeed, if one were to make a spray dried formulation for delivery by dry powder inhaler, one would not be concerned with the Freund's spraying anomalies in the nebulizer. These are mutually exclusive technologies and problems. Bernstein does not provide anything that the combination of Freund and Richards lacks.

The Examiner alleges that Freund teaches administration of dry powders. (Page 8, Final office action.) The Abstract suggests that the product administered is an aqueous solution. The Examiner is asked to present a citation for the allegation.

In addition, none of the cited references discloses dry powder particles wherein the aerodynamic diameter of the actual particles in an 8 stage cascade impactor is actually measured, much less teach the fine particle fraction limitation. All of the dry particle formulations of trospium tested in the present application have an FPF of at least 50% and provided the greatest protection (greater than 20 hours) from bronchoconstriction even as compared to the aqueous composition of trospium tested (see page 15, lines 23-30 and Figure 3). Therefore, it is unexpected that the presently claimed dry powder formulations of claim 8 and all claims dependent thereon (claims 10-13, 15 and 18-21) would have the presently claimed duration of therapy. The cited combination of references does not disclose or suggest that duration of therapy or the claimed fine particle fraction of the trospium particle of claim 8 and all of its dependent claims.

Claim 10

Claim 10 depends on claim 8 and requires the trospium to be spray dried. While Bernstein generally says that a preferred method of making its sustained release microparticles is by spray drying, the specifics of spray drying a trospium formulation to achieve a sustained release formulation (which does not rely on the addition of a matrix material) is not taught. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. As such, claim 10 is not obvious over this combination of references.

Claim 11

Claim 11 depends on claim 10 and limits the tap density of the formulation. While Bernstein teaches a single budesonide formulation with a tap density that falls within the scope of the claim, the rejection fails to explain why one would select this density and spray dry a trospium formulation. Further, the data suggests that increasing porosity decreases the long acting property over a 5.5 hour period. Fig. 1. This data does not support the allegation that a long acting formulation of trospium can be made in a light porous particle. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. As such, claim 11 is not obvious over this combination of references.

Claim 12

Claim 12 depends on claim 11 and requires the mass median aerodynamic diameter of the particles to be less than 5 microns. Bernstein simply does not teach, nor does it teach the desirability to combine, low porosity and small aerodynamic diameters with spray dried trospium to achieve long acting therapy. Clearly, Freund and Richards fail to teach these limitations as well. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. As such, claim 12 is not obvious over this combination of references.

Claim 13

Claim 13 depends on claim 12 and further requires the trospium to be spray dried with a phospholipid and/or leucine. While Bernstein generally says that a lipid, as well as many other materials, can be used in making the microparticles of the specification, he does not disclose the specific combination of trospium, phospholipid and/or leucine. Certainly, Freund does not suggest that his solutions can tolerate other divergent excipients. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. Richards is not relevant either. As such, claim 13 is not obvious over this combination of references.

Claim 15

Claim 15 depends on claim 14, which was not rejected. The cited combination of references does not disclose or suggest the claimed features of **claim 15** which depends upon *claim 14 which is believed to be allowable* and recites the relative amounts of trospium in addition to the leucine of claim 14 that provides a 10 hour duration of therapy as is shown in the Examples and Figures 1-3 of the specification. Claim 15 requires at least 70% leucine and less than 10% trospium. Nowhere in this rejection does it suggest that leucine is an excipient to be combined with trospium in this concentration. Bernstein does not teach or suggest the specific combination of trospium and leucine. Certainly, Freund does not suggest that his solutions can tolerate other divergent excipients. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. Richards is not relevant either. As such, claim 15 is not obvious over this combination of references.

Claim 18

Claim 18 depends on claim 16, which was not rejected. Thus, claim 18 is, on its face, non-obvious for the reasons claim 16 is non-obvious. Claim 18 requires a specific dose of a specific formulation having about 5% trospium, 5-10% phospholipid and about 85-90% leucine. Nowhere in this rejection is this formulation suggested. Bernstein does not teach or suggest the specific combination or dose. Certainly, Freund does not suggest that his solutions can tolerate other divergent excipients. Further, for the reasons set forth

above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. Richards is not relevant either. As such, claim 18 is not obvious over this combination of references.

Claims 19 and 20

Claims 19 and 20 also depend on claim 16, which was not rejected. Thus, claims 19 and 20 are, on its face, non-obvious for the reasons claim 16 is non-obvious. Claims 19 and 20 require a specific pharmacokinetic profile of a specific formulation having about 5% trospium, 5-10% phospholipid and about 85-90% leucine. Nowhere in this rejection is this formulation suggested, nor is the pharmacokinetic profile. Bernstein does not teach or suggest the specific combination or dose. Certainly, Freund does not suggest that his solutions can tolerate other divergent excipients. Further, for the reasons set forth above with respect to claim 8, one would not combine these teachings of Bernstein with the teachings of Freund. Richards is not relevant either. As such, claims 19 and 20 are not obvious over this combination of references.

Claim 21

Claim 21 depends on claim 8 and requires a method where the formulation is administered once a day. Given the fact that none of the references teach a formulation with a long acting therapy for trospium, the claim cannot be considered obvious. While Bernstein does teach once a day formulations, how to make a trospium once a day is simply not taught.

Claims 22-26

Claims 22-26 include all of the limitations of claim 1 and are discussed in detail above. Likewise for the reasons discussed above with regard to the rejection over Freund and Richards, claims 22-26 are also not made obvious by the combination of Freund with Richards and Bernstein. As discussed above, Bernstein is no more relevant than Richards with regard to its teaching of combination therapies. There is no motivation provided by any of the references to seek a formulation of trospium, particularly one that provides 10 hours of therapy as discussed above, and there is no suggestion or motivation to combine

trospium with any other active agent while maintaining the claimed duration of therapy of trospium. Withdrawal of the rejection of claims 22-26 under this section is respectfully requested.

Claim 27

Claim 27 includes all of the limitations of claims 1, 22, 23, 24 and 26 and recites that the composition further comprises a spray dried formulation of trospium, formoterol, leucine and optionally a phospholipid (compare also claims 7 and 13). Freund is directed to aqueous formulations and does not disclose spray dried formulations of any drugs and particularly a spray dried formulation of trospium in combination with formoterol, leucine and optionally a phospholipid. Richards and Bernstein discuss spray dried formulations of various drugs but neither discloses nor suggests a spray dried formulation of trospium, formoterol, leucine and optionally a phospholipid. The skilled person would not be motivated based on Freund to produce a spray dried formulation comprising trospium, formoterol and leucine and optionally a phospholipid having a 10 hour effective therapy with any expectation of success. Withdrawal of the rejection of claim 27 under this section is respectfully requested.

(8) Claims Appendix

See Attached

(9) Evidence Appendix

See Attached

(10) Related Proceedings Appendix

See Attached

The Conclusion

As the Examiner has failed to establish a prima facie case of obviousness and the unexpected results achieved by the present invention, Appellants request reversal of the rejection and allowance of the application.

Respectfully submitted,

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8. Claims Appendix

1. (Original) A method for treating a disease characterized by a constrictive airway comprising administering to a patient in need thereof via inhalation a pharmaceutical composition comprising trospium, wherein said patient achieves an effective therapy for at least 10 hours.

2. (Original) The method of Claim 1 wherein said disease is chronic obstructive pulmonary disease.

4. (Original) The method of Claim 1 wherein said composition comprises a dose of trospium of between about 200 to 800 mcg.

5. (Original) The method of Claim 1 wherein said composition comprises an aqueous solution of trospium hydrochloride.

6. (Original) The method of Claim 1 wherein said composition comprises a particulate formulation comprising trospium.

7. (Original) The method of Claim 1 wherein said composition comprises a dry particulate formulation of trospium wherein said formulation is administered with a dry powder inhaler.

8. (Original) The method of Claim 1 wherein said composition comprises a dry particulate formulation of trospium characterized by a fine particle fraction of at least 50% and wherein said formulation is administered with a dry powder inhaler.

10. (Original) The method of Claim 8 wherein said trospium formulation comprises spray dried trospium.

11. (Original) The method of Claim 10 wherein said trospium formulation has a tap density of less than 0.4 g/cm^3.

12. (Original) The method of Claim 11 wherein said trospium formulation has a mass mean aerodynamic diameter of less than 5 microns.

13. (Original) The method of Claim 12 wherein said trospium formulation further comprises leucine, a phospholipid or combinations thereof.

14. (Original) The method of Claim 13 wherein said formulation comprises at least about 70% by weight of leucine.

15. (Original) The method of Claim 14 wherein said formulation contains less than about 10% by weight of trospium.

16. (Original) The method of Claim 14 wherein said formulation comprises about 5% by weight trospium hydrochloride; between about 5 and 10% by weight of phospholipid and between about 85 and 90% by weight of leucine.

18. (Original) The method of Claim 16 wherein the dose of trospium administered is about 200 to 800 mcg.

19. (Previously Presented) The method of Claim 16 wherein the patient achieves an effective therapy for at least about 15 hours.

20. (Previously Presented) The method of Claim 16 wherein the patient achieves an effective therapy for at least about 24 hours.

21. (Original) The method of Claim 8 wherein the formulation is administered once per day.

22. (Original) The method of Claim 1 further comprising the administration of a second active agent.

23. (Original) The method of Claim 22 wherein the second active agent is a beta-2 agonist.

24. (Original) The method of Claim 23 wherein the second active agent is formoterol.

25. (Original) The method of Claim 23 wherein the second active agent is administered separately from the trospium formulation.

26. (Original) The method of Claim 24 wherein the second active agent is incorporated into the trospium formulation.

27. (Original) The method of Claim 24 wherein the composition comprises a spray dried formulation comprising trospium, formoterol, leucine and, optionally, a phospholipid.

9. Evidence Appendix

None

10. Related Proceedings Appendix

None